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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/937,066	09/20/2001	Hazire Oya Alpar	41577/263691	4735
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JOHN S. PRATT, ESQ KILPATRICK STOCKTON, LLP 1100 PEACHTREE STREET ATLANTA, GA 30309			EXAMINER HINES, JANA A	
			ART UNIT 1645	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

09/937,066

Applicant(s)

ALPAR ET AL.

Examiner

Ja-Na Hines

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 April 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3,5,6,11-17,20-22,37 and 40 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3,5,6,11-17, 20-22, 37 and 40 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Amendment Entry

1. The amendment filed April 3, 2007 has been entered. Claims 1 and 3 have been amended. Claims 2, 4, 7-10, 18-19, 23-36 and 38-39 have been cancelled. Claims 1, 3, 5-6, 11-17, 20-22, 37 and 40 are under consideration in this office action.

Withdrawal of Rejections

2. The following rejections have been withdrawn in view of applicants' amendments and arguments:

- a) The objection of claims 18-19 and 36 under 37 CFR 1.75(c);
- b) The rejection of claims 1 and 3 under 35 U.S.C. 102(b) as being anticipated by Kotze et al., (International J. of Pharm., 1997);
- c) The rejection of claim 1, 3-4, 6, 11-18 and 36-37 under 35 U.S.C. 103(a) as being unpatentable over Kotze et al., (International J. of Pharm., 1997) in view of Eyles.
- d) The rejection of claims 1, 3-6, 11-12, 16, 18-21 and 36-37 under 35 U.S.C. 103(a) as being unpatentable over Kotze et al., (International J. of Pharm., 1997) in view of Illum (WO 97/20576 published June, 1997); and
- e) The rejection of claim 1, 3- 6, 11-12, 20-22 and 37 under 35 U.S.C. 103(a) as being unpatentable over Kotze et al., (International J. of Pharm., 1997) in view of Duncan et al., (WO 94/20070 published September 1994).

Response to Arguments

3. Applicant's arguments with respect to claims 1, 3, 5-6, 11-17, 20-22, 37 and 40 have been considered but are moot in view of the new ground(s) of rejection.

New Grounds Of Objection and Rejection

Claim Objections

4. Claim 37 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 37 is drawn to a composition that comprises a biologically active agent which is able to produce an immune response in an animal to which it is administered; however Claim 1 already recites a biologically active agent which is able to produce an immune response in an animal to which it is administered. Therefore clarification is required to overcome the objection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. Claims 1, 3, 6, 11-17, 37 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over in view of Eyles (1998. Vaccine. Vol.16(7):698-707) in view of Kotze et al., (J. of Pharm. Sci. Vol.88(2):253-257. Published online 12/5/1998).

Claim 1 is drawn to a pharmaceutical composition comprising a biologically active agent that is capable of generating a protective immune response in an animal and a polycationic carbohydrate wherein the polycationic carbohydrate is a water-soluble alkylated chitosan selected from the group consisting of trimethyl chitosan with a degree of quaternization that is at least 20% and N-carboxymethyl chitosan or a salt thereof. Claim 3 is drawn to the pharmaceutical composition wherein the alkylated chitosan is trimethylchitosan with a degree of quaternization that is at least 40%. Claim 6 is drawn to the pharmaceutical composition further comprising a first material capable of forming particles, wherein the pharmaceutical composition is in the form of particles. Claim 11 is drawn to the particles comprising microspheres, microparticles or liposomes. Claim 12 is drawn to the particles being microparticles. Claim 13 is drawn to the first material capable of forming particles is a polymeric material which has a molecular weight of 100kDa or more. Claim 14 is drawn to the first material capable of forming particles comprises poly-(L-lactide). Claim 15 is drawn to the ratio of the first material capable of forming particles to the polycationic carbohydrate is from 99:1 to 9:1 w/w. Claim 16 is drawn to the biologically active agent is capable of generating a protective immune response against tetanus, diphtheria, or *Yersinia pestis*. Claim 17 is drawn to the biologically active agent comprising a combination of the V antigen of *Y. pestis* or an immunologically active fragment thereof, and the F1 antigen of *Y. pestis* or

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an immunologically active fragment thereof. Claim 37 is drawn to a biologically active agent which is able to produce an immune response in an animal to which it is administered. Claim 40 is drawn to the pharmaceutical composition wherein the alkylated chitosan is trimethyl chitosan with a degree of quaternization that is at least 60%.

Eyles et al., teach a pharmaceutical composition comprising poly-(L-lactide) microspheres co-encapsulated with *Yersinia pestis* V and F1 subunits that confer protection from pneumonic plague in mice (page 699, col.2). Eyles et al., teach that the F1 antigen confers resistance to phagocytosis and both F1 and V antigens are protective, although there is an additive effect in the combination (page 698, col.2). It is noted that the F1 peptide subunit is a glycoprotein. The commercially purchased poly-(L-lactide) has a molecular weight of 100 kDa and was used in a modified double emulsion solvent evaporation method (page 699, col.2). It is noted that Eyles et al., teach the use of such microparticles and/or spheres and the associated chemical compounds and the claimed ratios. No more than routine skill is required to change the concentration or ratio of well known compositions and such changes do not impart patentability to the composition.

Eyles et al., teach effective vaccination requires affecting or utilizing mucosal surfaces as portals of entry (page 698-699, col.2-1). Furthermore Eyles et al., teach that mucosal vaccination advantageously offers some degree of the induction of systemic immunity in concert with local responses due to translocation of antigenic material (page 699, col.1). Eyles teach that simple mucosal applications are ineffective because of

enzymatic or chemical destruction, combined with poor absorption; therefore encapsulation of antigenic material within microparticulate polymeric carriers such as poly-DL-lactide protect the vaccines from degradation and enhance mucosal and systemic absorption (page 699, col.1). However Eyles et al., do not teach pharmaceutical compositions comprising trimethyl chitosan chloride that is at least 20% quarternized.

Kotze et al., teach pharmaceutical compositions comprising N-trimethyl chitosan chloride (TMC) that is 61.2% quarternized (abstract). Kotze et al., teach that TMC with higher degrees of quarternization are more effective as absorption enhancers and increase the paracellular transport of compounds (page 253, col.2). Kotze et al., teach TMC is able to significantly increase the transport of hydrophilic compounds and peptide drugs (page 253, col.2). Kotze et al., teach that TMC interacts with components of glycoproteins (page 256, col.2).

Therefore it would have been prima facie obvious at the time of applicants' invention to modify the pharmaceutical composition comprising a biologically active agent as taught by Eyles et al., wherein the modification incorporates the use of trimethyl chitosan chloride that is at least 20% quarternized as taught by Kotze et al., in order to increase absorption across mucosal surfaces. One of ordinary skill in the art would be motivated to modify the microparticle compositions as taught by Eyles et al., because Eyles et al., teach that effective compositions capable of generating a protective immune response require utilizing mucosal surfaces as portals of entry; thus one of ordinary skill in the art would have a reasonable expectation of success in

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providing microparticle compositions with further significantly increased mucosal absorption which is beneficial to the recipient without the disadvantage of enzymatic or chemical destruction, combined with poor absorption. No more than routine would have been required to modify the composition of Eyles et al., by incorporating the trimethyl chitosan chloride that is at least 20% quarternized, because Kotze et al., teach higher degrees of quarternization are more effective as absorption enhancers and increase the paracellular transport of peptide compounds and/or glycoproteins, while Eyles teach et al., that the F1 antigen is both a peptide drug and a glycoprotein. Furthermore, the limitations drawn to the ratios of particles to the polycationic carbohydrate, trimethyl chitosan are viewed as merely optimizing the experimental parameters and not imparting patentability; thus no more than routine skill would have been required to change the concentration in the well known compositions as taught by Eyles et al., in view of Kotze et al.

6. Claims 1, 3, 6, 11-12, 16, 37 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Illum (WO 97/20576 published June, 1997) in view of Kotze et al., (J. of Pharm. Sci. vol.88(2):23-257. Published online 12/5/1998).

Claim 1 is drawn to a pharmaceutical composition comprising a biologically active agent that is capable of generating a protective immune response in an animal and a polycationic carbohydrate wherein the polycationic carbohydrate is a water-soluble alkylated chitosan selected from the group consisting of trimethyl chitosan with a degree of quaternization that is at least 20% and N-carboxymethyl chitosan or a salt

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thereof. Claim 3 is drawn to the pharmaceutical composition wherein the alkylated chitosan is trimethylchitosan with a degree of quaternization that is at least 40%. Claim 6 is drawn to the pharmaceutical composition further comprising a first material capable of forming particles, wherein the pharmaceutical composition is in the form of particles. Claim 11 is drawn to the particles comprising microspheres, microparticles or liposomes. Claim 12 is drawn to the particles being microparticles. Claim 16 is drawn to the biologically active agent is capable of generating a protective immune response against tetanus, diphtheria, or *Yersinia pestis*. Claim 37 is drawn to a biologically active agent which is able to produce an immune response in an animal to which it is administered. Claim 40 is drawn to the pharmaceutical composition wherein the alkylated chitosan is trimethyl chitosan with a degree of quaternization that is at least 60%.

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Illum teaches vaccine compositions comprising one or more biologically active agents capable of generating a protective immune response in an animal, an effective adjuvant and the polycationic carbohydrate, chitosan (page 1, lines 1-6). Illum teaches suitable antigens include tetanus toxoid and diphtheria toxoid (pages 4-5, lines 23-1). Illum teaches the pharmaceutical compositions are formulated in the form of microspheres (page 6, lines 22-24). Illum teaches that chitosans are known as mucosal absorption enhancers and upon administration, chitosan enhances the immune response of antigens and provides an enhanced effect upon the host (page 3, lines 1-6). However Illum does not teach pharmaceutical compositions comprising trimethyl chitosan chloride that is at least 20% quarternized.

Kotze et al., teach pharmaceutical compositions comprising N-trimethyl chitosan chloride (TMC) that is 61.2% quarternized (abstract). Kotze et al., teach that TMC with higher degrees of quarternization are more effective as absorption enhancers and increase the paracellular transport of compounds (page 253, col.2). Kotze et al., teach TMC is able to significantly increase the transport of hydrophilic compounds (page 253, col.2).

Therefore it would have been prima facie obvious at the time of applicants' invention to modify the pharmaceutical composition comprising a biologically active agent as taught by Illum, wherein the modification incorporates the use of trimethyl chitosan chloride that is at least 20% quarternized as taught by Kotze et al., in order to increase absorption across mucosal surfaces. One of ordinary skill in the art would be motivated to modify the compositions as taught by Illum, because Illum teach the need

for chitosans, which are well known mucosal absorption enhancers that also enhance the immune response of antigens; thereby providing a reasonable expectation of success. Thus one of ordinary skill in the art would have a reasonable expectation of success in providing compositions having higher degrees of quarternization, since Kotze et al., teach that a 61.2% quarternized trimethyl chitosan are more effective as absorption enhancers. No more than routine would have been required to modify the composition of Illum et al., to instead incorporate the trimethyl chitosan chloride that is at least 20% quarternized, because Kotze et al., teach that higher degrees of quarternization increase the paracellular transport of compounds. Finally it would have been advantageous to incorporate trimethyl chitosan that is at least 20% quarternized in the pharmaceutical composition, in order to achieve an enhanced effect upon the host.

7. Claims 1, 3, 5-6, 11-12, 20-22, 37 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Duncan et al., (WO 94/20070 published September 1994) in view of Kotze et al., (J. of Pharm. Sci. vol.88(2):23-257. Published online 12/5/1998).

Claim 1 is drawn to a pharmaceutical composition comprising a biologically active agent that is capable of generating a protective immune response in an animal and a polycationic carbohydrate wherein the polycationic carbohydrate is a water-soluble alkylated chitosan selected from the group consisting of trimethyl chitosan with a degree of quaternization that is at least 20% and N-carboxymethyl chitosan or a salt thereof. Claim 3 is drawn to the pharmaceutical composition wherein the alkylated chitosan is trimethylchitosan with a degree of quaternization that is at least 40%. The

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pharmaceutical of claim 5 is drawn to the pharmaceutical composition further comprising a cationic polyamino acid. Claim 6 is drawn to the pharmaceutical composition further comprising a first material capable of forming particles, wherein the pharmaceutical composition is in the form of particles. Claim 11 is drawn to the particles comprising microspheres, microparticles or liposomes. Claim 12 is drawn to the particles being microparticles. The pharmaceutical of claim 20 is drawn to the pharmaceutical composition further comprising a cationic polyamino acid and/or a cationic pluronic. Claim 21 is drawn to the pharmaceutical composition further comprising a cationic pluronic. Claim 22 is drawn to the composition comprising particles of the cationic pluronic which are surface modified with the polycationic carbohydrate. Claim 37 is drawn to a biologically active agent which is able to produce an immune response in an animal to which it is administered. Claim 40 is drawn to the pharmaceutical composition wherein the alkylated chitosan is trimethyl chitosan with a degree of quaternization that is at least 60%.

Duncan et al., teach compositions comprising: i) biologically active agents, such as immunogens or antigens at pages 4-5 para.1, ii) an adjuvant chemical having adjuvant properties wherein the adjuvants include PluronicTM block copolymers also known as cationic pluronics and polyamino acids such as polyarnithine at pages 9-10, para. 1; and iii) an acceptable carrier such as a mucoadhesive at page 6, para.1.

Duncan et al., further teach that an enhancement in the immune response is observed when the adjuvant is combined with the immunogen and mucoadhesive (pages 10-11, para.2). The antigens are more immunogenic when they are incorporated into the

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polymeric microparticles, nanoparticles or liposomes (page 2, para.4). However Duncan et al., do not teach pharmaceutical compositions comprising trimethyl chitosan chloride that is at least 20% quarternized.

Kotze et al., teach mucoadhesive pharmaceutical compositions comprising N-trimethyl chitosan chloride (TMC) that is 61.2% quarternized (abstract). Kotze et al., teach that TMC with higher degrees of quarternization are more effective as absorption enhancers and increase the paracellular transport of compounds (page 253, col.2). Kotze et al., teach TMC is able to significantly increase the transport of hydrophilic compounds (page 253, col.2).

Therefore, it would have been prima facie obvious at the time of applicants' invention to have used the known trimethyl chitosan composition as taught by Kotze et al., and modify the compositions to include the biologically active antigen and adjuvant agents capable of generating a protective immune response and providing the compositions in a microparticle formulation as taught by Duncan et al., in order to enhance the mucoadhesive properties. One of ordinary skill in the art would have a reasonable expectation of success by modifying the pharmaceutical compositions as taught by Duncan et al., because Duncan et al., teach the need for mucoadhesive which provide further enhancement in the immune response. Thus one of ordinary skill in the art would have a reasonable expectation of success in providing compositions having higher degrees of quarternization, since Kotze et al., teach that trimethyl chitosan chloride that is at least 60% quarternized is more effective as absorption enhancers. No more than routine would have been required to modify the composition

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of Duncan et al., to instead incorporate the trimethyl chitosan chloride that is at least 20% quarternized, because Kotze et al., teach that higher degrees of quarternization increase the paracellular transport of compounds, into the pharmaceutical composition of Duncan which already comprises a mucoadhesive combined with biological active antigens and cationic pluronic in microparticle formation to achieve enhanced mucosal absorption. Finally it would have been advantageous to incorporate trimethyl chitosan that is at least 20% quarternized in the pharmaceutical composition, in order to achieve an enhanced effect upon the host.

Conclusion

8. No claims allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

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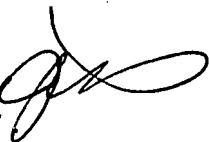
the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached on Monday-Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Jeffery Siew, can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ja-Na Hines
June 5, 2007




JEFFREY SIEW
SUPERVISORY PATENT EXAMINER